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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/448,042	11/23/1999	STANLEY N. LAPIDUS	EXT-023	4602

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/448,042	Applicant(s) LAPIDUS ET AL.	
	Examiner Carla Myers	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,10-12,15,18-20 and 24-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,10-12,15,18-20 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. The request filed on July 24, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/448,042 is acceptable and a CPA has been established. An action on the CPA follows.

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,4,10, 15,18,20 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok in view of JP 09187277 (abstract, July 22, 1997).

Kwok teaches a method for determining the presence of a target nucleotide by adding to a DNA sample a primer covalently labeled with a fluorescent dye, performing primer extension in the presence of a dideoxynucleotide covalently labeled with a fluorescent dye capable of being activated through fluorescent energy transfer to produce a detectable fluorescent signal when the dideoxynucleotide is incorporated into the extension product, determining the presence of the fluorescent signal and thereby determining the presence of the target nucleotide (see abstract, Figure 1, column 3; lines 21-33 and examples 1-2). Kwok et al teaches the limitation of claim 4

by teaching that the extension reaction could be performed in the presence of at least two different dideoxynucleotides (see example 5, column 21, line 40 through column 23). Kwok teaches the limitation of claim 10 by teaching the use of 6-carboxy-X rhodamine, N,N,N,N-tetramethyl-6-carboxyrhodamine, 6-carboxy-X-rhodomine, and fluorescein (Table 1) and teaches that any number of fluorophore combination can be use in their method (column 7, lines 52-60). Kwok teaches the use of their method to detect a nucleic acid mutation (see examples 4 and 5) (limitation of claim 18) and to detect a single nucleotide polymorphism (see example 2) (limitation of claim 20).

While Kwok does teach that the method can be performed on a nucleic acid sample obtained from virtually any source (column 9, lines 35-44), Kwok does not specifically teach exposing the primer to a stool, urine or blood sample. However, JP09187277 discloses a method for performing nucleic acid extension and PCR amplification directly on a sample of whole blood.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Kwok to a patient blood sample of JP09187277 in order to make the claimed invention as a whole because JP09187277 taught that a nucleic acid PCR method could be performed on nucleic acid from whole blood without isolation of the nucleic acid from the whole blood sample such that the ordinary artisan would have been motivated to analyze the blood sample using the method of Kwok which provided more sensitive and specific results. The ordinary artisan would have been motivated to have modified the method of Kwok to use the whole blood sample of JP 09187277 in order to have achieved the expected result of reducing the number of method steps required to obtain the nucleic acid for the

Kwok method with the expectation that the Kwok method would have been successful on this sample since JP09187277 showed that nucleic acid could be detectably amplified by exposure of a primer to the whole blood sample.

4. Claims 1,4,10, 15, 18, 20, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. in view of Gillespie

Kwok et al. teaches a method for determining the presence of a target nucleotide by adding to a DNA sample a primer covalently labeled with a fluorescent dye, performing primer extension in the presence of a dideoxynucleotide covalently labeled with a fluorescent dye capable of being activated through fluorescent energy transfer to produce a detectable fluorescent signal when the dideoxynucleotide is incorporated into the extension product, determining the presence of the fluorescent signal and thereby determining the presence of the target nucleotide (see abstract, Figure 1, column 3; lines 21-33 and examples 1-2). Kwok teaches the limitation of claim 4 by teaching that the extension reaction could be performed in the presence of at least two different dideoxynucleotides (see example 5, column 21, line 40 through column 23). Kwok teaches the limitation of claim 10 by teaching the use of 6-carboxy-X rhodamine, N,N,N,N-tetramethyl-6-carboxyrhodamine, 6-carboxy-X-rhodomine, and fluorescein (Table 1) and teaches that any number of fluorophore combination can be use in their method (column 7, lines 52-60). Kwok teaches the use of their method to detect a nucleic acid mutation (see examples 4 and 5) (limitation of claim 18) and to detect a single nucleotide polymorphism (see example 2) (limitation of claim 20).

While Kwok does teach that their method can be performed on a nucleic acid sample obtained from virtually any source (column 9, lines 35-44), Kwok does not specifically teach

exposing the primer to a stool, urine or blood sample. However, Gillespie discloses a method for a nucleic acid hybridization detection method on a sample of whole blood (column 49, 51-52) or stool (column 50) without an additional nucleic acid isolation step. Gillespie also taught that their method applies to many different biological samples including blood, lymph, urine, saliva, pieces of tissue (column 7, lines 62-67).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Kwok to a patient blood or stool sample of Gillespie in order to make the claimed invention as a whole because Gillespie taught that a nucleic acid hybridization method could be performed on nucleic acid from whole blood or stool without isolation of the nucleic acid from the whole blood or stool sample such that the ordinary artisan would have been motivated to analyze the blood sample using the method of Kwok which provided more sensitive and specific results. The ordinary artisan would have been motivated to have modified the method of Kwok to use the whole blood or stool sample of Gillespie in order to have achieved the expected result of reduce the number of method steps required to obtain the nucleic acid for the Kwok method with the expectation that the Kwok would have been successful on this sample since Gillespie showed that nucleic acid could be detectably hybridized and detected by exposure of a labeled probe to the whole blood or stool sample.

5. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok in view of JP09187277 or Kwok in view of Gillespie, as applied to claims 1,4,10, 15,18,20 and 25, and further in view of Lu et al. (abstract).

The teachings of Kwok and JP0918277 and Kwok and Gillespie are presented above. The combined references do not specifically teach applying the method to the detection of mutations in the p53, apc, or ras genes. However, Lu et al. teach that the p53, apc and ras genes are all known to be oncogenes involved in a number of different cancers.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the nucleotide detection method of Kwok in view of JP09187277 or Kwok in view of Gillespie to the detection of mutations in p53, apc and ras because Lu taught that these genes were known to be involved in cancer and that the detection of mutations was important for the diagnosis and prognosis of cancer.

6. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok in view of JP09187277 or Kwok in view of Gillespie, as applied to claims 1,4,10, 15,18,20 and 25 above, and further in view of O'Dell et al. (Clin. Chem. (1998) 44(1): 183-185.

The teachings of Kwok and JP09187277 and Kwok and Gillespie are presented above. The combined references do not teach using a sample from a pooled patient population.

However, O'Dell et al. taught a method of analyzing a target nucleic acid for the presence of mutations associated with disease by screening pooled DNA samples.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Kwok in view of JP09187277 or Kwok in view of Gillespie to the screening of pooled DNA samples as taught by O'Dell because O'Dell taught that screening pooled DNA samples allowed the efficient and cost-effective processing of a large number of specimens.

RESPONSE TO ARGUMENTS

7. In the response of Paper No. 11, filed July 24, 2002, Applicants traversed this rejection by stating that in the method of Kwok, the fluorescent signal is produced only upon denaturation and release of the primer extension product from the target nucleic acid. It is argued that Kwok does not teach a method in which upon incorporation of the dideoxynucleotide into a double-stranded nucleic acid product resulting from the primer extension reaction, the acceptor molecule is proximate to the donor molecule such that the acceptor molecule is activated through fluorescent energy transfer from said donor molecule so as to produce a detectable fluorescent signal without self-quenching.

Applicants arguments have been fully considered but are not persuasive for the following reasons. Firstly, it is noted that Applicants claims do not exclude performing a step of denaturation because the claims are drawn to methods which "comprise" the recited steps and thereby the methods may include additional steps (i.e., the claims do not specifically require detecting the fluorescent signal generated by the double-stranded nucleic acid product). Secondly, it is noted that the claims in the Kwok patent do not recite a step of separating the labeled primer extension product from the target nucleic acid prior to detecting the fluorescent signal. Thirdly, the method of Kwok does in fact result in a detectable fluorescent signal upon incorporation of the dideoxynucleotide into the double-stranded nucleic acid product. It is acknowledged that in one embodiment Kwok teaches that the position of the 2 fluorophores may be selected so that upon release of the primer extension product, fluorescent energy transfer occurs between the donor and acceptor fluorophore to generate a fluorescent signal. However, Kwok also teaches that the probe may bind immediately 3' to the polymorphic site at which the

labeled dideoxynucleotide is to be incorporated (column 5). Kwok also teaches that the probe may be labeled either at the terminus or internally. Further, the reference teaches that the transfer of energy is most efficient when the donor and acceptor fluorophore are separated at a distance of about 3.5 nucleotides, but that at least 16% of the efficiency of the fluorescent signal remains when the acceptor and donor fluorophore are separated by a distance of 13 nucleotides (column 9). Accordingly, in the method of Kwok, the extension of the flourophore-labeled probe with the fluorophore-labeled dideoxynucleotide would necessarily result in the presence of an acceptor molecule that is proximate to a donor molecule such that the acceptor molecule is activated through fluorescent energy transfer from the donor molecule to produce a detectable fluorescent signal.

NEW GROUNDS OF REJECTION

8. Claims 1, 4, 10, 15, 18, 20 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (Proceedings of the National Academy of Sciences, USA (September 1997) 94: 10756-10761; reference "C93") in view of JP 09187277 (abstract, July 22, 1997).

Chen teaches a method for determining the presence of a target nucleotide by adding to a DNA sample a primer covalently labeled with a fluorescent dye, performing primer extension in the presence of a dideoxynucleotide covalently labeled with a fluorescent dye capable of being activated through fluorescent energy transfer to produce a detectable fluorescent signal when the dideoxynucleotide is incorporated into the extension product, determining the presence of the fluorescent signal and thereby determining the presence of the target nucleotide (see page 10756). Most importantly, Chen teaches that the "fluorescent intensities were acquired during the annealing/extension phase of the primer extension cycles" (see page 10757, column 2). Real

time fluorescent measurements were obtained directly following incorporation ~~incorporation~~ of the fluorescently labeled dideoxynucleotide into the double-stranded primer extension product (page 10758). Thereby, Chen teaches a method in which "upon incorporation of said dideoxy nucleotide into a double-stranded nucleic acid product resulting from primer extension, said acceptor molecule is proximate to said donor molecule so as to produce a detectable fluorescent signal without self-quenching".

Chen teaches the limitation of claim 4 by teaching that the extension reaction could be performed in the presence of at least two different dideoxynucleotides (page 10756). Chen teaches the limitation of claim 10 by teaching the use of 6-carboxy-X rhodamine and N,N,N,N-tetramethyl-6-carboxyrhodamine (TAMRA) fluorophores (page 10757, column 2). Chen teaches the use of their method to detect a nucleic acid mutation or single nucleotide polymorphism (see, for example, page 10756).

Chen exemplifies the disclosed method using isolated genomic DNA. Chen does not specifically teach directly exposing the primer to a stool, urine or blood sample. However, JP09187277 discloses a method for performing nucleic acid extension and PCR amplification directly on a sample of whole blood.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Chen to a patient blood sample of JP09187277 in order to make the claimed invention as a whole because JP09187277 taught that a nucleic acid PCR method could be performed on nucleic acid from whole blood without isolation of the nucleic acid from the whole blood sample such that the ordinary artisan would have been motivated to analyze the blood sample using the method of Chen which provided more sensitive

and specific results. The ordinary artisan would have been motivated to have modified the method of Chen to use the whole blood sample of JP 09187277 in order to have achieved the expected result of reducing the number of method steps required to obtain the nucleic acid for the Chen method with the expectation that the Chen method would have been successful on this sample since JP09187277 showed that nucleic acid could be detectably amplified by exposure of a primer to the whole blood sample.

9. Claims 1, 4, 10, 15, 18, 20, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (Proceedings of the National Academy of Sciences, USA (September 1997) 94: 10756-10761; reference "C93") in view of Gillespie.

Chen teaches a method for determining the presence of a target nucleotide by adding to a DNA sample a primer covalently labeled with a fluorescent dye, performing primer extension in the presence of a dideoxynucleotide covalently labeled with a fluorescent dye capable of being activated through fluorescent energy transfer to produce a detectable fluorescent signal when the dideoxynucleotide is incorporated into the extension product, determining the presence of the fluorescent signal and thereby determining the presence of the target nucleotide (see page 10756). Most importantly, Chen teaches that the "fluorescent intensities were acquired during the annealing/extension phase of the primer extension cycles" (see page 10757, column 2). Real time fluorescent measurements were obtained directly following incorporation of the fluorescently labeled dideoxynucleotide into the double-stranded primer extension product (page 10758). Thereby, Chen teaches a method in which "upon incorporation of said dideoxy nucleotide into a double-stranded nucleic acid product resulting from primer extension, said

acceptor molecule is proximate to said donor molecule so as to produce a detectable fluorescent signal without self-quenching".

Chen teaches the limitation of claim 4 by teaching that the extension reaction could be performed in the presence of at least two different dideoxynucleotides (page 10756). Chen teaches the limitation of claim 10 by teaching the use of 6-carboxy-X rhodamine , N,N,N,N-tetramethyl-6-carboxyrhodamine (TAMRA), and fluorescein fluorophores (page 10757, column 2). Chen teaches the use of their method to detect a nucleic acid mutation or single nucleotide polymorphism (see, for example, page 10756).

Chen exemplifies the disclosed method using isolated genomic DNA. Chen does not specifically teach directly exposing the primer to a stool, urine or blood sample. However, Gillespie discloses a nucleic acid hybridization detection method on a sample of whole blood (column 49, 51-52) or stool (column 50) without an additional nucleic acid isolation step. Gillespie also taught that their method applies to many different biological samples including blood, lymph, urine, saliva, and pieces of tissue (column 7, lines 62-67).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Chen to a patient blood or stool sample of Gillespie in order to make the claimed invention as a whole because Gillespie taught that a nucleic acid hybridization method could be performed on nucleic acid from whole blood or stool without isolation of the nucleic acid from the whole blood or stool sample such that the ordinary artisan would have been motivated to analyze the blood sample using the method of Chen which provided more sensitive and specific results. The ordinary artisan would have been motivated to have modified the method of Chen to use the whole blood or stool sample of

Gillespie in order to have achieved the expected result of reduce the number of method steps required to obtain the nucleic acid for the Chen method with the expectation that the Chen method would have been successful on this sample since Gillespie showed that nucleic acid could be detectably hybridized and detected by exposure of a labeled probe to the whole blood or stool sample.

10. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen in view of JP09187277, as applied to claims 1,4,10, 15,18,20 and 25, or Chen in view of Gillespie, as applied to claims 1,4,10, 15, 18, 20, and 25-26, and further in view of Lu et al. (abstract).

The teachings of Chen and JP0918277 and Chen and Gillespie are presented above. The combined references do not specifically teach applying the method to the detection of mutations in the p53, apc, or ras genes. However, Lu et al. teach that the p53, apc and ras genes are all known to be oncogenes involved in a number of different cancers.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the nucleotide detection method of Chen in view of JP09187277 or Chen in view of Gillespie to the detection of mutations in p53, apc and ras because Lu taught that these genes were known to be involved in cancer and that the detection of mutations was important for the diagnosis and prognosis of cancer.

11. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen in view of JP09187277, as applied to claims 1,4,10,15, 18, 20 and 25, or Chen in view of Gillespie, as applied to claims 1,4,10, 15, 18, 20, 25 and 26 above, and further in view of O'Dell et al. (Clin. Chem. (1998) 44(1): 183-185.

The teachings of Chen and JP09187277 and Chen and Gillespie are presented above. The combined references do not teach using a sample from a pooled patient population.

However, O'Dell et al. taught a method of analyzing a target nucleic acid for the presence of mutations associated with disease by screening pooled DNA samples.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Chen in view of JP09187277 or Chen in view of Gillespie to the screening of pooled DNA samples as taught by O'Dell because O'Dell taught that screening pooled DNA samples allowed the efficient and cost-effective processing of a large number of specimens.

12. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen in view of JP09187277, as applied to claims 1,4,10, 15,18,20 and 25, or Chen in view of Gillespie, as applied to claims 1,4,10, 15,18,20, 25 and 26 above, and further in view of Ju (U.S. Patent No. 5,952,180).

The teachings of Chen and JP09187277 and Chen and Gillespie are presented above. Chen teaches labeling the dideoxynucleotides with 6-carboxy-X rhodamine and N,N,N,N-tetramethyl-6-carboxyrhodamine (TAMRA), and labeling the oligonucleotide with fluorescein (page 10757, column 2). Chen does not specifically teach labeling the dideoxynucleotide or oligonucleotide with 6-carboxyfluorescein.

Ju teaches methods of detecting a nucleic acid using fluorescent resonance energy transfer. Ju teaches that the fluorescent energy transfer labels may consist of 6-carboxy-fluorescein (FAM) as a donor and 6-carboxyrhodamine (ROX) as an acceptor (see, for example, Figure 2 and column 2).

In view of the teachings of Ju, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Chen so as to have specifically used the donor-acceptor pair of 6-carboxy-fluorescein and 6-carboxyrhodamine to label the oligonucleotide and dideoxynucleotide because Ju teaches that these labels can be used effectively together in FRET assays to generate a detectable signal and thereby could be used effectively in the method of Chen to detect the presence of a target nucleotide.

13. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok in view of JP09187277, as applied to claims 1, 4, 10, 15, 18, 20 and 25, or Kwok in view of Gillespie, as applied to claims 1, 4, 10, 15,18,20, 25 and 26 above, each further in view of Ju (U.S. Patent No. 5,952,180).

The teachings of Kwok and JP09187277 and Kwok and Gillespie are presented above. Chen teaches labeling the dideoxynucleotides with 6-carboxy-X rhodamine and N,N,N,N-tetramethyl-6-carboxyrhodamine (TAMRA), and labeling the oligonucleotide with fluorescein (see, for example, Table 1). Kwok does not specifically teach labeling the dideoxynucleotide or oligonucleotide with 6-carboxyfluorescein.

Ju teaches methods of detecting a nucleic acid using fluorescent resonance energy transfer. Ju teaches that the fluorescent energy transfer labels may consist of 6-carboxy-fluorescein (FAM) as a donor and 6-carboxyrhodamine (ROX) as an acceptor (see, for example, Figure 2 and column 2).

In view of the teachings of Ju, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kwok so as to have specifically used the donor-acceptor pair of 6-carboxy-fluorescein and 6-carboxyrhodamine to

label the oligonucleotide and dideoxynucleotide because Ju teaches that these labels can be used effectively together in FRET assays to generate a detectable signal and thereby could be used effectively in the method of Kwok to detect the presence of a target nucleotide.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

October 15, 2002

CARLA J. MYERS
PRIMARY EXAMINER